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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/620,514	07/16/2003	Ricardo M. Attar	D0287 NP	3956

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EXAMINER	
HAMA, JOANNE	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 12/29/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/620,514	ATTAR ET AL.	
	Examiner	Art Unit	
	Joanne Hama, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 July 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *16 July 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This Application, filed July 16, 2003, claims priority to U.S. Provisional Application 60/396,501, filed July 17, 2002.

Claims 1-14 are under consideration.

Information Disclosure Statement

Applicant filed Information Disclosure Statements (IDS) on May 24, 2004 and December 11, 2003. All references cited on the IDSes have been considered. It is noted that reference AK on page 3 of the IDS submitted December 11, 2003 has two references cited. Applicant is requested to list these references separately.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-14 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a credible, specific and substantial utility or a well established utility. According to the Revised Utility Examination Guidelines, see the Federal Register, Vol. 66, No. 4, pp. 19092-1099 (January 5, 2001), also available at http://uspto.gov/web.menu.utility.pdf, the following definitions of credible, specific, and substantial apply.

A credible utility is one that a person of ordinary skill in the art would accept as currently available. An assertion is considered credible unless (a) the logic underlying

the assertion is seriously flawed, or (b) the facts upon which the assertion is based are inconsistent with the logic underlying the assertion. Credibility as used in this context refers to the reliability of the statement based on the logic and facts that are offered by the Applicant to support the assertion of utility. A credible utility is assessed from the standpoint of whether a person of ordinary skill in the art would accept that the recited or disclosed invention is currently available for such use.

A specific utility is one that is specific to the subject matter claimed. This contrasts with a general utility that would be applicable to the broad class of the invention.

A substantial utility is one that defines a real world use. Utilities that require or constitute carrying out further research to identify or reasonably confirm a real world context of use are not substantial utilities. Research that involves studying the properties of the claimed product itself does not constitute a substantial utility.

See also MPEP 2107-2107.02, and *Brenner, Comr. Pats. v. Manson*, 148 USPQ 689 (US SupCt 1966).

The instant claims are drawn to a transgenic non-human mammal whose genome comprises a nucleic acid construct, wherein said construct comprises a reporter nucleic acid encoding a reporter operably linked to a promoter comprising an androgen response element (ARE), and said construct further comprises an androgen receptor nucleic acid sequence encoding an androgen receptor, and wherein expression of said reporter nucleic acid is regulated by expression of said androgen receptor nucleic acid. The specification identifies the following uses for the claimed

transgenic non-human mammals, cells, and methods: the use of the transgenic non-human mammal or cells from the transgenic non-human mammal to study the tissue selective activity of pharmacological agents as well as the activity of the androgen receptor in different organs of males and females (specification, page 5, 2nd parag.) and 2) use of the transgenic animals to identify selective androgen receptor modulators that can act as antagonists or agonists in different tissues containing the androgen receptor (specification, page 8, 3rd parag.). Regarding the nucleic acid constructs, the specification only provides a single use for these constructs, which is to produce a mouse comprising in its genome a nucleic acid construct comprising a nucleic acid sequence encoding a reporter protein operably linked to a promoter comprising an androgen response element, said construct further comprising a nucleic acid sequence encoding an androgen receptor, and wherein the expression of the nucleic acid sequence encoding a reporter protein is controlled by the androgen receptor.

In regards to asserted utility 1), as identified above, the stated utility of the transgenic non-human mammals to study the activity of the androgen receptor in different organs of males and females does not constitute a real world utility and therefore is not a substantial utility, but rather represents further research on the product to identify or reasonably confirm a real world utility. As stated in the Guidelines set forth above, research that involves studying the properties of the claimed product itself does not constitute a substantial utility. Further, such an asserted utility constitutes a general, rather than a specific utility, as all transgenic overexpression non-human mammals can be used to study the effects of the gene overexpression. With regards to the other

issue of asserted utility 1), to study the tissue selective activity of pharmacological agents, nothing in the specification indicates that any of the claimed transgenic non-human mammals have any phenotype. Therefore, it is unclear how the claimed transgenic non-human mammals can be used to study tissue selective activity of pharmacological agents. Therefore, asserted utility 1) does not meet the standard for a specific and substantial utility.

In regards to asserted utility 2), as identified above, the specification does not teach that any of the claimed non-human mammals have any phenotype resulting from activity of the androgen receptor that is overexpressed in their cells. Thus, it is presently unclear how an artisan could use the claimed transgenic non-human mammals to identify any antagonists or agonists in different tissues containing the androgen receptor. Thus, asserted utility 2) does not meet the standard for a specific and substantial utility.

Since the specification does not assert a specific and substantial utility that meets the requirements of 35 U.S.C. 101 for the claimed transgenic non-human mammals, the constructs, cells obtained from the transgenic non-human mammal, also lack a specific and substantial utility. It thus follows that the methods of making and using the claimed transgenic non-human mammals have not utility as well.

Thus, in view of the discussion above, the skilled artisan would not find any of the asserted utilities of the transgenic non-human mammal, cells derived from the transgenic non-human mammal, targeting construct, or cells obtained from the mammal encompassed by the claims to be specific and substantial, or well-established.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-14 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (*Wands*, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state

of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

The claims are drawn to a transgenic non-human mammal whose genome comprises a nucleic acid construct, wherein said construct comprises a reporter nucleic acid encoding a reporter operably linked to a promoter comprising an androgen response element (ARE), and said construct further comprises an androgen receptor nucleic acid sequence encoding an androgen receptor, and wherein expression of said reporter nucleic acid is regulated by expression of said androgen receptor nucleic acid, the cells obtained from the claimed transgenic non-human mammal, a construct used to generate the claimed transgenic non-human mammals, and methods of making and using the claimed transgenic non-human mammals in a screen for modulators of the androgen receptor. The specification teaches a transgenic mouse comprising in its genome, a transgene construct comprising SEQ ID NO. 1. The specification teaches the various components that comprise SEQ ID NO. 1 (specification, page 9, Figs. 1-6). While the specification teaches that transgenic mice were generated and that the mice express luciferase (specification, examples 3 and 4), the specification does not provide guidance that the mice have any phenotype associated with the overexpression of the transgene construct. This is an important issue for an artisan to know for the following reason.

The specification generally teaches phenotypes associated with changes in androgen levels (e.g. castration, which causes a cessation of testosterone, leads to a

decrease in the aggression in animals, or low testosterone levels have been associated with fatigue, or that infusion of testosterone into the coronary arties of men with coronary artery disease results in an acute significant increase in coronary blood flow (specification, page 3)), or generally teaches that there are relationships between androgens and disease (specification, page 4). However, nothing in the specification teaches that the claimed transgenic non-human mammals encompassed by the claims exhibit any symptoms associated with androgen receptor overexpression. An artisan would need to know what phenotypes are exhibited by these transgenic non-human mammals because one aspect of the intended use of the claimed non-human mammals is for finding pharmacological agents that modulate the androgen receptor (e.g. see specification, page 7, 2nd parag.). Nothing in the specification teaches that the mouse described in the Examples or any other transgenic non-human mammal encompassed by the claims exhibits any phenotype caused by the overexpression of androgen receptor. As such, because the specification does not teach that any of the claimed non-human mammals encompassed by the claims exhibit any phenotype, an artisan could not use the claimed non-human mammals to screen for any pharmaceutical agents.

In addition to this issue of intended use, the claims are not enabling for the full breadth of any transgenic non-human mammal whose genome comprises a nucleic acid construct, wherein said construct comprises a reporter nucleic acid encoding a reporter operably linked to a promoter comprising an androgen response element (ARE), and said construct further comprises an androgen receptor nucleic acid sequence encoding

an androgen receptor, and wherein expression of said reporter nucleic acid is regulated by expression of said androgen receptor nucleic acid for the following reason. At the time of filing, the art teaches examples that making transgenic animals is unpredictable. For example, the art teaches that there is unpredictability in using transgene constructs amongst different animals. Hammer et al.,1990, Cell, 6: 1099-1112, created both transgenic mice and rats expressing the human HLA-b27 gene and beta-2 microglobulin. Although both transgenic animals bearing the HLA-b27 gene expressed the gene, transgenic mice did not show any HLA-b27 associated disease, whereas the transgenic rats demonstrated most of the HLA-b27 related diseases (Hammer, et al., page 1099, col. 2, lines 20-28). This shows that the integration of a transgene into an alternative species may result in widely different phenotype responses even in animals of the same species. It should also be pointed out that Hammer et al.'s teaching indicates that the unpredictability in using a transgene construct could stem from the fact that use of promoters in transgenic constructs are unpredictable and that the gene of interest expressed in heterologous animals do not behave predictably. With regards to the promoter, Cowan et al., 2003, Xenotransplantation, 10: 223-231 teach that promoters of three human genes, ICAM-2, hCRPs, and PECAM-1, which are predominantly expressed in vascular endothelium in mice and pigs. When tissue specific expression was measured, it was found that while mice showed a distinct expression profile of the three human genes, the tissue expression profiles of the three human gene promoters were distinctly different in pigs. The authors concluded that "promoter performance in mice and pigs was not equivalent," and that "the weak

expression driven by the human ICAM-2 promoter in pigs relative to mice suggests the need for additional regulatory elements to achieve species-specific gene expression in pigs. In the case of the gene of interest behaving unpredictably, Hammer et al., 1986, J. of Anim. Sci., 63: 269-278 teach that while transgenic mice that overexpressed human growth hormone exhibited enhanced growth, transgenic pigs that expressed human growth hormone did not increase weight gain (Hammer et al., page 276, under "Effect of Foreign GH on Growth"). Thus, while the specification provides guidance on what nucleic acid sequences were used in the transgenic mice of the Examples, the specification, in light of the teachings in the art, does not enable an artisan overcome the issues of unpredictability in the art, in order to practice the art of transgenesis for its full breadth.

In view of the lack of guidance, working examples, breadth of the claims, and state of the art at the time of the claimed invention was made, it would have required undue experimentation to make and/or use the invention as claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 4-7, 11, 12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 4 recites the limitation "mouse" in claim 1. There is insufficient antecedent basis for this limitation in the claim as there is no "mouse" in claim 1. Claims 5-7 depends on claim 4.

Claim 11 uses the phrase, "target mouse." It is unclear what this term means and nothing in the specification provides any description of what a "target mouse" is. In addition to this, claim 11, step a) uses the phrase, "solating a fertilized egg." It is unclear what this means.

Claim 12 recites the limitation "transgenic mouse" in claim 1. There is insufficient antecedent basis for this limitation in the claim. There is no mouse in claim 1.

Conclusion

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joanne Hama, Ph.D. whose telephone number is 571-272-2911. The examiner can normally be reached Monday through Thursday and alternate Fridays from 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, Ph.D. can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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JH